REMARKS

The specification has been amended to cross-reference related applications and to correct a minor typographical error. The amendment to the paragraph beginning at page 2, line 14, corrects a typographical error as is evidenced by the printout of McCarty (Med. Hypotheses 56:286-289, 2001; "McCarty"), a copy of which is enclosed as Exhibit 1. McCarty is cited in the specification at page 2, lines 18-19, of the English language specification and is entitled "Prospects for Glycerol-Rescued Hypoglycemia as a Cancer Therapy." No new matter has been added by the present amendment.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 23 December 2005

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1: Med Hypotheses. 2001 Mar;56(3):286-9.

ELSEVIER FULL-TEXT ARTICLE

Prospects for glycerol-rescued hypoglycemia as a cancer therapy.

McCarty MF.

Pantox Laboratories, San Diego, California 92109, USA.

Most neoplasms are dependent on glucose as their primary fuel, and their ambient glucose levels tend to be rather low owing to wasteful aerobic glycolysis and poor perfusion. Previous attempts to starve tumors by inducing hypoglycemia have foundered on the fact that the CNS and other tissues have high glucose requirements. Burt has proposed that, inasmuch as hypoglycemia-sensitive normal tissues can make efficient use of glycerol, whereas many or most cancers cannot, hypoglycemic cancer therapy may be feasible if glycerol is concurrently infused. Unfortunately, when Burt used 3-mercaptopicolinate to inhibit gluconeogenesis and thereby induce hypoglycemia in fasted tumor-bearing subjects, infused glycerol served as gluconeogenic substrate, raising the serum glucose level. Agents which inhibit gluconeogenesis more distally - namely at the level of glucose-6-phosphatase or of fructosediphosphatase - may prevent the gluconeogenic response to glycerol, making glycerol-rescued hypoglycemic therapy of cancer feasible. In fact, certain new drugs being developed for diabetes therapy - chlorogenic acid derivatives and 'compound A' - are potent inhibitors of glucose-6-phosphatase, and both AICA riboside and 2,5-anhydro-D-mannitol have potential as clinical inhibitors of fructosediphosphatase. Insulin also can inhibit gluconeogenesis, both proximally and distally, and can potentiate hypoglycemia by promoting muscle glucose uptake; thus, coinfusion of high-dose insulin and of glycerol may represent an alternative viable strategy. Further research along these lines may enable glycerol-rescued hypoglycemia to become a feasible cancer therapy that has particular value as a complement to antiangiogenic measures. Copyright 2001 Harcourt Publishers Ltd.

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